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SPECIAL ARTICLE

Cancer Drugs in the United States: *Justum Pretium*—The Just Price

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INTRODUCTION

In 2011, health care spending in the United States was estimated at $2.7 trillion,[1] making it the sixth largest economy in the world, larger than the national budget of France. National health care spending is approximately 18% of the US gross domestic product, more than $8,000 per person, compared with 6% to 9% in Europe and elsewhere, with apparently similar patient outcomes. Total Medicare expenditures in 2011 were $549 billion.[2] A study comparing the Canadian universal health care program in older patients with the Medicare program in the United States suggested that adopting more-prudent health care strategies could have saved $2.56 trillion from 1980 to 2009, or approximately one fifth of our national debt, without compromising benefit.[3]

In the debate about health care and Medicare solvency, strategies that reduce health care costs without compromising treatment efficacy and patient safety should be explored. Several experts have addressed health care costs in excellent analyses and editorials,[4-9] but their efforts have not translated into concrete decisions and results that benefit patients, providers, insurers, or payees. However, an interesting exception occurred recently when Bach et al,[10] in a *New York Times* editorial, compared the efficacy and cost of two anticancer agents—ziv-aflibercept (Zaltrap; sanofi-aventis, Bridgewater, NJ) and bevacizumab (Avastin; Genentech, South San Francisco, CA)—in the treatment of metastatic colorectal cancer. After noting ziv-aflibercept had similar efficacy but was twice the cost of bevacizumab, they stated it would be excluded from their hospital formulary.[10] Within 1 week, sanofi-aventis, the company producing ziv-aflibercept, reduced its price by 50%. Thus, expert review of anticancer therapies for their cost-benefit ratios may influence institutional usage and drug pricing while preserving a healthy profit margin for pharmaceutical companies.

Aristotle is credited to be the first to discuss the relationship between price and worth in his book *Justum Pretium*—the just price. Sixteen centuries later, Saint Albert the Great and Saint Thomas Aquinas refined Aristotle's argument. Their conclusion: of moral necessity, price must reflect worth. In the context of cancer therapy, the prices of new anticancer agents seem to be decided by pharmaceutical companies according to what the market will bear. There is little correlation between the actual efficacy of a new drug and its price, as measured by cost-efficacy (CE) ratios, prolongation of patient life in years, or quality-adjusted life-years (QALYs).[7] Compared with a decade ago, the price range of new anticancer agents has more than doubled, from $4,500 to more than $10,000 per month.[4,5] Of the 12 anticancer drugs approved by the US Food and Drug Administration (FDA) in 2012, only three prolonged survival, two of them by less than 2 months. Yet nine were priced at more than $10,000 per month. Many so-called targeted therapies have been priced between $6,000 to 12,000 per month, or approximately $70,000 to 115,000 per patient annually (Table 1).[11] However, novel or reformulated chemotherapy drugs like pralatrexate (Folotyn; Allos Therapeutics, Westminster, CO; $120,000 per course), omacetaxine (Synribo; Teva Pharmaceuticals, North Wales, PA; $28,000 for induction, $14,000 for monthly treatments), and pegylated asparaginase (Oncaspar; Sigma-Tau Pharmaceuticals, Gaithersburg, MD; $22,000 per course) are also expensive. Hillner and Smith[7] suggested that profiteering (ie, making profit by unethical methods, such as raising prices after natural disasters) could be applied to this recent trend, where a life-threatening disease is the natural disaster.

Pharmaceutical companies justify the high price of drugs as necessary to support investment in research and development. The often-cited cost of bringing anticancer drugs to FDA approval is $1 billion.[12] This figure is roughly calculated by dividing total expenditures on research and development by the number of agents that receive FDA approval. However, this figure may be inflated, because it includes ancillary expenses, salaries, bonuses, and other indirect costs not related to research or development[13] as well as an 11% compounded discount rate over 10 years based on stock market returns on capital investment.[14] Other independent estimates

Table 1. Cost of Targeted Therapy

Agent	Target	FDA-Approved Indication	Monthly or Per-Cycle Cost
Imatinib	BCR-ABL	CML	$6,982
Dasatinib	BCR-ABL	CML	$9,817
Nilotinib	BCR-ABL	CML	$9,163
Bosutinib	BCR-ABL	CML	$9,817
Sorafenib	VEGF, multikinase	RCC, HCC	$10,555
Sunitinib	VEGF, multikinase	RCC, GIST	$11,957
Everolimus	mTOR	RCC, breast	$8,984
Temsirolimus	mTOR	RCC	$6,355
Pazopanib	VEGF, multikinase	RCC	$7,778
Bevacizumab	VEGF	RCC, colon, lung	$11,684
Erlotinib	EGFR	Pancreatic, NSCLC	$5,756
Cetuximab	EGFR	Colon, head/neck	$24,092
Lapatinib	HER2	Breast	$5,120
Trastuzumab	HER2	Breast	$5,295
Brentuximab	CD30	Hodgkin lymphoma	$16,768*
Crizotinib	ALK1	NSCLC	$11,946
Ipilimumab	CTLA-4	Melanoma	$36,540†
Vemurafenib	BRAF	Melanoma	$12,282
Ruxolitinib	JAK2	Myelofibrosis	$8,400
Lenalidomide	IMID	Myeloma	$10,103

NOTE. Data adapted.[11]
Abbreviations: ALK1, anaplastic lymphoma kinase 1; CD30, cluster of differentiation 30; CML, chronic myeloid leukemia; CTLA-4, cytotoxic T lymphocyte–associated antigen 4; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; GIST, GI stromal tumor; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; IMID, immunomodulating drug; JAK2, Janus kinase 2; mTOR, mammalian target of rapamycin; NSCLC, non–small-cell lung cancer; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor receptor.
*Up to 16 cycles; $270,000 for 1 year of therapy.
†Up to four doses; $146,000 total.

of cost of drug development put the figure as low as 4% to 25% of this estimate.[15-17]

Allowing the producer-dominated market to set drug prices has spiraled the cost of cancer drugs out of control. In this analysis, we highlight examples of the cost benefit of different anticancer agents and suggest scenarios for reduced drug pricing, while preserving the profit-making incentive, by linking price to a true measure of quality: preservation and meaningful prolongation of life.

HOW DID WE GET HERE? ILLUSTRATIVE EXAMPLES

Consider three examples that illustrate the problem of benefit and price. The first involves tyrosine kinase inhibitors (TKIs) in the therapy of chronic myeloid leukemia (CML). TKIs in CML are examples of newer, more expensive drugs that offer benefit for early surrogate measures of prognosis, but not for long-term survival, over a less expensive and soon to be generic first generation TKI (ie, imatinib). The introduction of imatinib has improved the 10-year survival rate in CML from 20% to 85%.[18] The drug price was $30,000 per year when it became available in 2001, but it had increased to $80,000 to $92,000 per year in 2012, a prime example of a drug being worth as much as it can be sold for. Even for a uniquely successful drug during its patent period, this is a disturbing trend,[19] because development costs for imatinib were falling, new indications were being added, and the patient pool was expanding dramatically.[20] Newer TKIs like dasatinib, nilotinib, and bosutinib benefit patients with disease resistant to imatinib. First-line randomized studies comparing these new TKIs with imatinib showed improvements in the early surrogate end points, including higher rates of complete cytogenetic, major molecular, and complete molecular responses as well as a reduction in the aggregate early rates of transformation to accelerated and blastic phases from 6% to 2.8%.[21,22] Whether this difference will continue on an annual basis or represents most of the benefit that will be gained from these early interventions remains to be defined with longer follow-up. However, none of the studies has shown a survival benefit for the new TKIs in front-line CML therapy, because they confer a favorable outcome in most patients when used as salvage therapy after imatinib failure. The current annual prices of nilotinib and dasatinib in the United States range from $115,000 to $124,000. For ponatinib, a third-generation TKI, the annual price is $138,000. Imatinib may become available in a generic formulation by January 2015, at which time the differential price between a generic imatinib and newer TKIs will be considerable ($2,000 to $10,000 $v >$ $100,000). Using newer-generation TKIs in the United States as front-line therapy (annual incidence, 5,000 patient cases; prevalence, 80,000 patients in 2014)[20] may cost up to $8.8 billion. Using generic imatinib as front-line therapy and a new-generation TKI when imatinib is no longer effective costs less than 10% of that. To justify the cost of second-generation TKIs in front-line therapy in all patients with CML, a significant difference in clinically relevant outcomes, such as survival, must be shown. This is unlikely, because the estimated 10-year survival with imatinib is 85%. Even minor but statistically significant differences in survival (eg, 3% to 5% difference in 10-year survival) need to be evaluated in relation to the total cost of these drugs. More appropriate strategies may involve generic imatinib as front-line therapy and newer TKIs for salvage. Alternatively, a reevaluation of the annual price of new TKIs in objective terms (CE, QALY gained, or other proposed end points) might be considered.

A second example is targeted therapies approved for the treatment of metastatic solid tumors. Most approvals have been given for higher objective response rates or statistically significant prolongation of progression-free survival (PFS), but only occasionally significant improvement in survival. A partial list of targeted therapies approved for different cancer subsets and their prices is provided in Table 1. In renal cell cancer alone, seven targeted therapies were approved between 2005 and 2012: sorafenib (2005), sunitinib (2006), temsirolimus (2007), everolimus (2009), bevacizumab (with interferon alfa; 2009), pazopanib (2009), and axitinib (2012).[23-28] All seven agents were associated with significant improvements in median PFS (range, 3 to 6 months), with or without minimal impact on survival, at a cost of $70,000 to $140,000 annually. Many experts argue survival in renal cell cancer may have improved, from a historical median of 12 to a median of 24 months, with the use of these targeted therapies and attribute the lack of a survival benefit in some studies to their crossover design. The Surveillance, Epidemiology, and End Results data do not support this argument.[29] In pancreatic cancer, the FDA approved erlotinib in 2005 based on statistically significant median survival prolongation of only 10 days.[30] Similar examples abound for FDA-approved targeted therapies in lung, GI, and other cancers. There has been little evaluation of the cost of these marginal gains, with discussions often erroneously confused with talk of so-called death panels and rationing of care.

A third example is therapies associated with long-term PFS and survival in a fraction of patients. Anti-CTLA4 blocking antibodies (ipilimumab) and B-RAF inhibitors (vemurafenib) in melanoma may produce impressive response rates (vemurafenib), with only a modest prolongation in PFS and survival, but importantly long-term PFS in a small but measurable fraction of patients, perhaps 20% to 25%.[31-33] Other new strategies may follow the same pattern, although this remains to be proven. In such instances, the price of these agents may be reasonably expected to be higher than agents that prolong survival minimally without significant longer-term survival or PFS effects.

WHAT CONTRIBUTES TO THE HIGH PRICES?

As the FDA approves new agents, pharmaceutical companies seem to analyze the market response to the most similar previous agent and to set the price of the new one somewhat higher. In a free market, the hope is that the drug price settles according to its real benefit. But in oncology, there seems to be little correlation between the benefit of a new drug and its price.[7] Although this approach of what the market will bear to drug pricing is most responsible for the spiraling prices, the cost of developing drugs has escalated, albeit not as dramatically as their prices.

Multiple factors have contributed to the increases in drug development costs, and some are beyond the control of pharmaceutical companies. One such uncontrolled factor is the increasing regulatory burden imposed by health agencies, including the National Institutes of Health, National Cancer Institute (NCI), FDA, and Office of Human Research Protection. Although the regulations on human research protection have not changed in 30 years, their interpretation by legal experts, government agencies, and institutional review boards has shifted drastically to conservative interpretations that in the opinion of many delay and obstruct cancer research and increase costs while adding little to patient protection.[34-39] A total of 300 to 600 regulatory steps, half of them judged unnecessary, are often required to initiate Cancer Therapy Evaluation Program–sponsored or cooperative group trials, with a median time of 400 to 700 days to initiation.[34-38] Although these regulatory burdens represent a genuine attempt to protect patients from harm, they are preventing many patients from entering clinical trials and are actually harming the individuals we hoped to protect.[39] They have also contributed to development costs such that it is now estimated that the cost per life-year saved is approximately $2.7 million (when a reasonable cost is valued at $100,000). Importantly, this added cost has translated into little if any added safety for patients.[39]

Whereas the foregoing may be uncontrolled, other factors adding to development costs are controllable. For example, lawyers and contract research organizations (CROs) have inserted themselves as necessary honest brokers between pharmaceutical companies and investigators. But many CROs are incentivized to expand the monitoring and regulatory steps rather than become cost efficient. The CRO industry revenue was projected to be $20 billion in 2010, representing approximately one third of total pharmaceutical and biotechnology research and development expenditures. Eighteen percent of trials were in the area of oncology. The cost per patient in a clinical trial has risen from an estimated $25,000 per patient in 2000 to as much as $100,000 in 2012. And most charges are not paying for any direct patient care. An example of such waste is the emerging QTc industry, which monitors QTc prolongations related to novel agents. In the cancer setting, this has contributed to redundant infrastructures and excessive work and expenses, without any protection for patients.[40] And all too often, pharmaceutical companies expend large sums of money in company-based or independent Certified Medical Education programs (eg, symposia, meetings, advisory boards) for the so-called education of oncologists on the benefit of new agents.[41]

Finally, two interesting phenomena that have nothing to do with drug development also add significantly to the drug prices. The first are laws that explicitly prohibit Medicare from negotiating lower cancer drug prices, although the Department of Veteran Affairs can and does negotiate significantly lower prices, approximately 25% to 50% lower than Medicare. When the government extended a much-needed Medicare drug benefit in 2003, a provision in the law was inserted (likely encouraged or guided by interest groups) that prohibited government (ie, Medicare) from bargaining for prices on drugs. The economist Dean Baker showed that a conservative- to middle-cost scenario could have saved Medicare approximately $50 to $80 billion per year if Medicare were allowed to negotiate drug prices. This is of course one of several ways our health care costs could be mitigated.[42] Negotiations of drug prices between governments and pharmaceutical companies are routine in Canada, most European nations, and most countries in the Middle East and Far East. For example, the prices of many TKIs are approximately 50% to 75% lower in these countries than in the United States. The second are the so-called pay-for-delay deals, in which pharmaceutical companies with brand-name drugs, the patents for which are expiring, pay companies to delay introduction of the generic versions.[43] Although this is a win-win situation for the drug companies, it represents a major loss to the US health care system and to patients. Bringing new generics to the market as soon as possible is estimated to have produced $1.06 trillion in savings over the last 10 years.[43]

PROPOSED SOLUTIONS

What is a just price for a new therapy? Can a price be morally set high enough that in aggregate, the strategy would bankrupt our health care system, not allow patients to afford the treatment, or cause personal bankruptcies? Should moral necessity obligate more affordable prices? Is it fair that one patient in the United States pays twice the price paid by another patient in the United States or two to four times the price paid by patients in other countries for the same drug? Should we pay less for drugs that produce only tumor reduction or PFS prolongation and more for drugs that alter the natural course of a disease and improve survival? Is market competition, left on its own, working well? Even when there are several competing drugs that offer similar benefits, competition does not seem to drive down the prices of brand-name drugs, leading skeptics to wonder if there is a possible collusive behavior to maintain a collective monopoly over drug prices among similar brand-name drugs.

A fair drug price must also reflect the reality of its true benefit and societal and personal costs. For example, anti–vascular endothelial growth factor inhibitors in metastatic colon cancer provide a median survival advantage of 1.4 months over standard of care, at a monthly cost of $5,000 to $11,000 per month. With a median overall survival from start of second-line therapy of 12 months, and a median duration of therapy of 12 to 14 months, the total cost translates into approximately $40,000 to $80,000 per patient per additional month of life. Most agree this is too high a price for such a modest benefit. Cetuximab was calculated to translate into an expenditure of $800,000 to prolong the life of one patient by 1 year.[8] In many developed countries, a price of less than $130,000 is considered sufficient to buy excellent care for an extra year of life.[44-47] In Great Britain, the National Institute for Health and Clinical Excellence established 30,000 pounds as a reasonable price for a QALY.

We believe that leaving the pricing of cancer drugs solely to pharmaceutical companies could bankrupt our health care system and Medicare and is unfair to our society and to those unfortunate individuals who develop cancers. Although many approaches can be taken to reduce drug prices, several seem evident.

We can start first with our self-inflicted wounds. Given that the elderly suffer from cancer disproportionately, Medicare should be able to negotiate the prices paid for drugs, as the Department of Veteran Affairs does. These negotiations may save Medicare an average of $50 to $80 billion per year.[42] We should ensure that relevant legislation does not conflict with the interests of the US government and patients, standing firm against lobbyists and associated interest groups. Paying generic manufacturers not to make newer versions of drugs coming off patent (ie, pay for delay) should also be eliminated.[43]

Researchers, academicians, and professional societies should demand better results and discontinue the practice of exulting marginal outcomes. The bar should be raised for expectations from new drugs, and hyping minor benefits of newer (more expensive) drugs over older (less expensive) ones should not be endorsed by tumor experts or professional societies unless such benefits truly reflect incremental value worth the differential price. This will also alleviate the pressure community oncologists feel to prescribe newer drugs promoted by experts at professional meetings.

A critical look at the cost of unnecessary research regulation is needed, with the goal of improving and streamlining protocol processes and eliminating unnecessary procedures. Reducing the barriers and intermediaries between researchers and pharmaceutical companies/NCI and eliminating any regulation that does not contribute to patient safety or quality of care will reduce the cost of research. The goal should be to bring the cost of research back down to $25,000 per patient. A consensus study committee appointed by the Clinical Trials Cooperative Group Program supported by the NCI developed a set of recommendations aimed at improving the speed and efficiency of trials, incorporating innovative science and trial design, improving prioritization in support of trials, and increasing patient participation. The recommendations were reported in 2011.[48] Ownership and championship of such efforts by regulators and researchers are necessary to make the cancer research process smoother, reduce its costs, and in turn help reduce the price of cancer drugs.

Finally, we must challenge the status quo that sets drug prices arbitrarily without regard to the real value of a drug. The value of a new cancer drug should be measured by one of several parameters: one, improving survival or PFS (particularly important as an early surrogate end point for indolent tumors); two, improving quality of life; three, reducing/alleviating adverse effects compared with similar approved drugs or reducing toxicities of cancer drugs; and four, reducing cost. To that end, we propose a value-based system for setting the initial price. Providers, regulators, patients and advocates, representatives of insurance and pharmaceutical companies, and other interested parties should all be involved in the discussion of initial pricing. The benefit quantified for FDA drug approval should be integral to drug pricing. Drug pricing could involve established measures of CE, life-years, or QALYs.[7] For most drugs, where tumor regression and prolongation of life are the goals, the amount of time that life is prolonged could be used as a simple measure of efficacy and guide drug pricing. A realistic range might consider a new drug that prolongs survival by more than 6 months or by more than one third of the life expectancy (eg, 12 months becomes $\geq$ 16 months, or 30 months is increased to $\geq$ 40 months) as extremely effective, with pricing at a range of $50,000 to $60,000. Similarly, an agent that improves long-term survival or PFS by 10% or more would fall into that category. On the other hand, drugs that demonstrate "statistically significant" survival benefits of 2 months or prolong life by less than 15% would be considered to have minimal efficacy and be priced much lower, perhaps below $30,000 per year. Drugs of intermediate effectiveness would be priced in between these two ranges. Similar measures could be implemented to value quality of life, reduction of toxicities or adverse effects, and cost.

Medical debt is now the most common cause of personal bankruptcy in the United States. Himmelstein et al[49] have estimated conservatively that 62% of all personal bankruptcies in 2007 were because of medical problems. Most debtors were well-educated homeowners with middle-class occupations; approximately 75% had health insurance. With out-of-pocket expenses of approximately 20%, many patients with cancer cannot afford their drugs and abandon treatment. By encouraging prices based on real value, drugs should become more affordable and their cost less burdensome to patients. Pharmaceutical companies will also be incentivized to develop better drugs that everyone can agree are really better.

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